ConCordix®

Nutra & ConCordix technology

A whitepaper on delivery forms

Introduction: Views on a Unique Delivery System for Dietary Supplements

The past decades it has become more important to focus on acceptable delivery systems for dietary supplements. A main factor is the growing number of consumers, and identification of a suitable dosage form has become key for many manufactures. Today, consumers can choose from a wide array of soft or hard gelatin capsules, coated and uncoated tables, powdered formulations or liquid tinctures. Research shows that delivery forms must have some crucial features, especially when it comes to long-term consumer commitment. Dietary supplements that have a set of attractive sensory properties including acceptable tastiness, texture, and smell are crucial in achieving consumer compliance [1]. In addition, the ease of administration has been given more attention from manufacturers since many traditional delivery forms are designed as large capsules or tablets. Easy intake plays an important role in pursuing groups who have difficulties swallowing large tables or capsules, while tastiness is an important factor for overall acceptance and compliance [2-6].

The ConCordix technology is a unique, patented delivery system for oral administration of both nutraceuticals and pharmaceuticals. This delivery system has a soft texture that is chewable, making it easier to ingest. It has a unique flavor and is sugar free. A specialized processing and packaging technology ensures shelf-life and good stability of active ingredients and the supplement [7]. Moreover, lipid- and water- soluble ingredients can be combined in a single supplement.

ConCordix offers a delivery form for dietary supplements that is innovative, and it provides tailor-made products with a large variety of ingredients, flavors, colors and shapes.

History of ConCordix

ConCordix is a patented technology owned by Vitux AS and was initially developed for the administration of omega-3 from fish oil supplements that had a better taste and provided a similar or improved uptake of active ingredients compared with traditional omega-3 supplements. Encouraging feedback was received since the distribution began.
The technology of ConCordix supplements consists of a unique method of processing and carrying active ingredients and large quantities of fish oil in one soft-chewable supplement. Continuous research brought new perspectives and created possibilities for new concepts adding vitamins, minerals, botanical extracts and essential oils.

A unique feature of the ConCordix technology is that both water- and oil-soluble ingredients can be added to one supplement. The exceptional packaging process ensures that all ingredients are protected against light and oxygen, keeping each supplement fresh and stable.

Today, ConCordix is serving millions of people across the globe, making health easier every day. The potential of this delivery form is tremendous, not only for fish oil supplements but across the entire nutraceutical spectrum. It is this potential that makes the ConCordix technology so unique and exciting serving all age groups from children to seniors addressing all kinds of health benefits.

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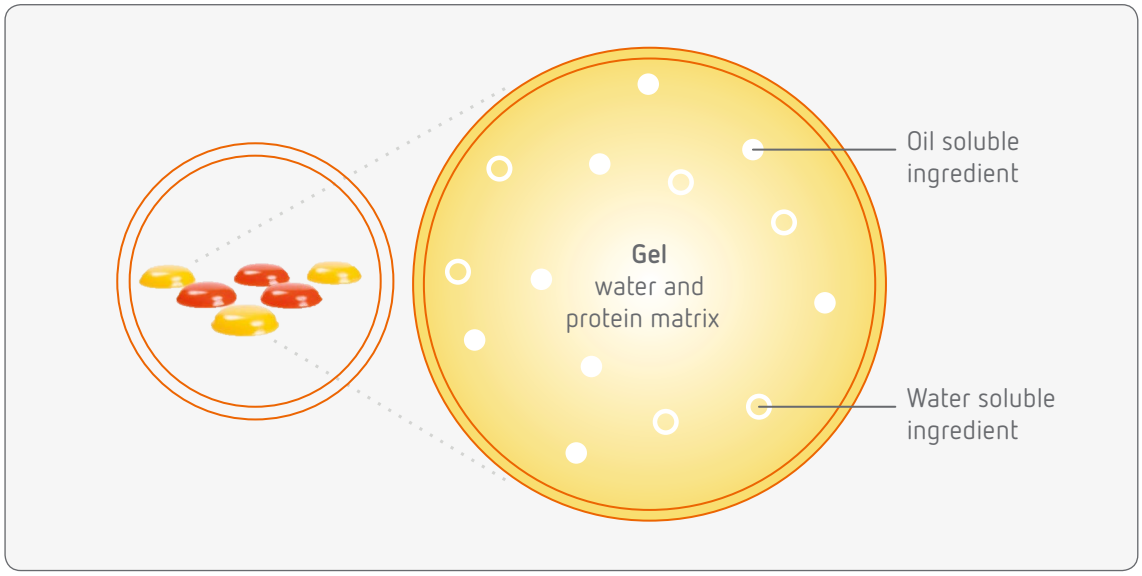
ConCordix Technology

The technology of ConCordix is based on thorough scientific research and cooperation with Universities. The formulation, packaging process, and flavoring are all part of this unique technology.

3.1 Formulation – Gelatin Matrix

The ConCordix technology makes it possible to combine oil- and water-soluble ingredients in one soft-chew. The uniqueness of this delivery system lies within its design which is a gelatin matrix in which lipid-soluble ingredients are emulsified and solubilized in a water-phase (water- soluble ingredients) and/or dispersed as particles that are immobilized inside the gelatin matrix (Figure 1).

Figure 1 Oil- and Water-Soluble Fraction of ConCordix



The gelatin is used to fixate the different active ingredients in a chewable delivery form that easily melts upon ingestion. The quick melting supports a fast release of active ingredients and eases absorption that may enhance bioavailability [7].

3.2 Packaging

The packaging process is designed to protect active ingredients against light and/or residual oxygen in ConCordix supplements, increase shelf-life and to ensure stability and remain water content during storage.

During the production of a ConCordix supplement oxygen is removed by multiple vacuuming steps and nitrogen blanketing. Thereafter the supplements are separately packed in an aluminum blister and sealed with an aluminum lidding foil. The foil protects each soft-chew against light, oxygen or moist that could affect the stability, freshness or shelf-life of the product. Oxygen may cause deterioration of ingredients, and in particular to fish-oils, resulting in the loss of potency, color change and a bad odor. Because each supplement is separately packed, opening one of the blisters will not impact the stability of the remaining supplements. This is a main advantage over supplements that are packed in a jar and exposed to oxygen every time the jar is opened.

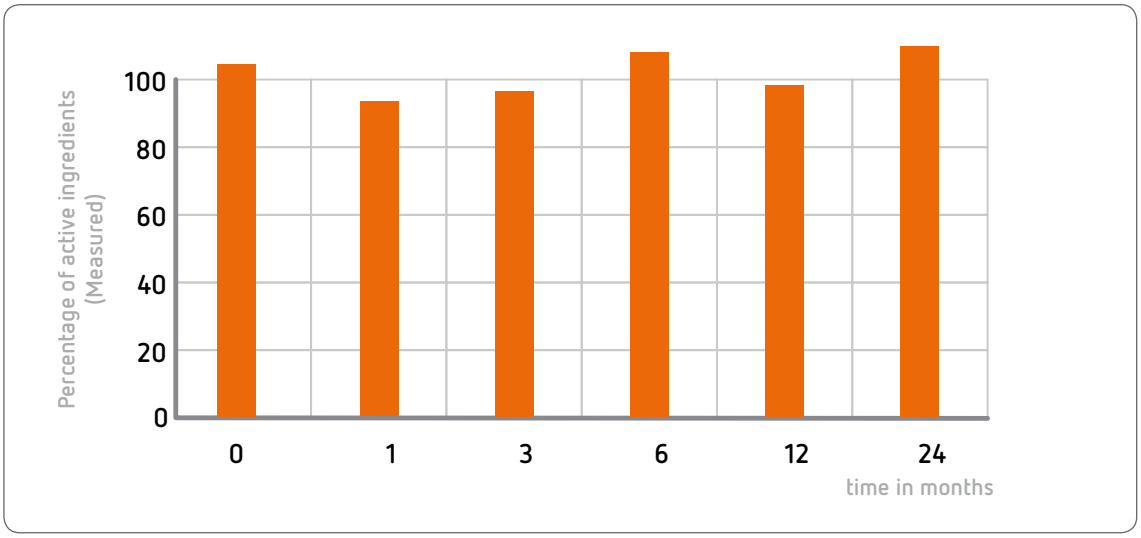
3.3 Stability

Stability is important for both the freshness of the soft-chew and the quality of active ingredients. Maintaining good stability ensures that active ingredients keep their potency at the end of shelf life. Poor stability results in the degradation of active ingredients, changes the taste or color, or causes the formation of degradation-products (oxidation products) [7]. Long-term stability tests (Figure 2) carried out to determine the oxidation status of ConCordix supplements with fish oil have shown exceptional stability with peroxide values well below 10 [7]. In addition, all new ingredients are subjected to a stability evaluation to ensure stability.

The exceptional stability we provide ensures:

- Reduced risk for degradation of ingredients
- Reduced risk for ingredient interactions
- Reduced risk of formation of oxidation products
- Improves shelf life
- Improves taste

Figure 2 Stability of ConCordix Soft-Chews over 24 Months



The percentage of active ingredients kept in the ConCordix soft-chew formulation over a period of 2 years, stored at 25°C.

3.4 Sensory Properties

Sensory properties include taste, texture and smell and are important for consumer acceptance and compliance. ConCordix supplements have a unique sensory profile, including the appearance, odor, taste and texture. A well-balanced combination of flavoring, sweeteners and acidulants are used to enhance the taste of the ConCordix soft-chews. The technology also provides exceptional taste masking properties, which is important to mask the distinct taste of certain active ingredients.

A primary factor directly related to compliance, is taste. If a dietary supplement has a well-accepted taste, it is known that consumers are more willing to remain compliant [1, 8, 9]. Studies conducted with ConCordix supplements in different age groups, revealed a high rate of acceptance, which contributes to a good compliance [6, 10, 11].

3.4.1 Flavoring

ConCordix supplements are developed with natural flavorings, using high quality aromas. All flavors are tested in laboratories using different combinations and concentrations of aromas to develop unique tastes. Each flavor used for ConCordix supplements is subjected to stability tests to ensure tastiness throughout the shelf-life.

The flavoring system used in each product is dependent on the composition of active ingredients. Ingredients as fish oil, zinc and some B-vitamins, have a distinct taste that needs to be masked to ensure a well-accepted taste. A range of flavors with specific masking abilities is designed for distinct tasting ingredients. The preferred flavor can be individually adjusted to each ConCordix soft-chew formulation, in combination with sweeteners and acidulants. A full list of natural flavors is presented at www.concordix.com/customized-formulations#our-flavours.

3.4.2 Sweeteners

We believe that dietary supplements should benefit health. Therefore, we use sweeteners instead of table sugar [12]. Xylitol and sorbitol are being used to give ConCordix supplements their sweetness. If ingredients require a more intense sweetness, stevia is used as a sweetness enhancer. Xylitol and sorbitol are known for their tooth-friendly properties and have similar to stevia, no effects on blood sugar [13]. In light of the growing overweight and diabetic population, this is an important advantage. Xylitol and sorbitol also support to keep the water activity low and to keep the product stable.
Acidulants such as malic acid and citric acid are used to balance the sweetness in the supplement and to enhance the tastiness. The sourness can be adjusted to some extent to match the flavor profile. Acidulants are also important to remain the pH-value and to provide good stability.

3.4.2.1 Sensory Property Studies

We strive to achieve a high compliance rate through providing excellent sensory properties. Sensory properties including tastiness, aftertaste, smell and texture of ConCordix supplements have been investigated in several age categories [6, 10, 11].
Adults who were given soft-chews with ibuprofen reported to 'like the taste' and compared the texture and taste with a sweet candy [11].

In a study with children who were administered with fish oil soft-chews or soft-chews without fish oil (comparator), demonstrated a high rate of acceptance. The taste masking properties were excellent since the results with fish oil were comparable with the comparator without fish oil [10].

Another study evaluated children's preference of several delivery forms. Taste and taste-masking were primary factors and the soft-chew was compared with three other delivery forms from different brands: liquid, soft-gel capsule, and a chewable capsule. Children rated the ConCordix soft-chew as best over the three other delivery forms (liquid, soft-gel capsule, chewable capsule) and a statistically significant difference for taste over all three other delivery forms was observed ($p < 0.05$) [6]. The results of that study inferred that the flavor combination with added sweeteners used for soft-chews results in an exceptional taste that is highly preferred by children [6].

Benefits

ConCordix supplements have several benefits that may contribute to produce dietary supplements that are suitable for all populations. Besides exceptional sensory properties that benefit consumer compliance, there are more benefits.

4.1 Easy Intake

Easy intake of supplements is an important characteristic for every manufacturer. When a supplement is too large, potential consumers are not likely to use it. Elderly and children tend to have the most difficulties with large sized delivery forms [2, 3, 14].

ConCordix supplements are designed to make ingestion easy. The soft-chews are chewable without causing early release of the active ingredients. The gelatin we use melts at body temperatures. After chewing shortly, the gelatin starts to dissolve which eases swallowing. Water is not needed for ingestion, which makes this delivery system also convenient for people 'on the go', travelers or military.

4.2 High Payload

Payload is important for the size of a supplement. This delivery system can carry volumes of lipid-soluble ingredients up to 50% and depending on the oil used, it can carry a larger than normal quantity of fish oil per dosage. The advantage is a lower dosing regimen and the size of the supplement can be reduced which increases consumer compliance and acceptance [10, 14].

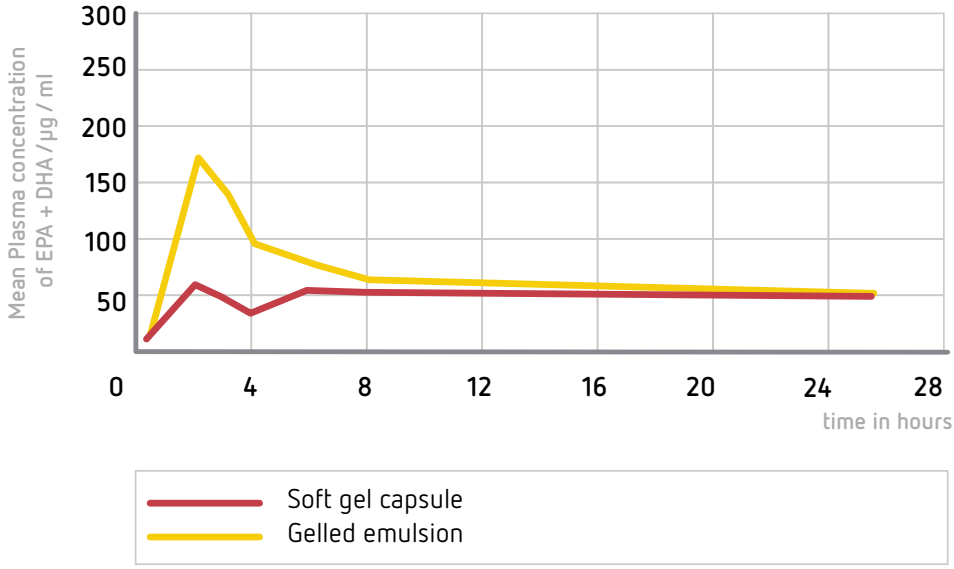
4.3 High Quality Ingredients

At Vitux A.S., only high-quality ingredients are used and come with a certificate of analysis. This means that all raw materials are scientifically corroborated and comply with EU regulatory safety standards. It ensures that all products are within costumer and regulatory specifications. Viux A.S. has an AA-rating for the BRC and advocates sustainability by being a member of 'Friend of the Sea' that uses only sustainable fish oil.
Some ingredients that are provided have been acknowledged with a health claim.
A list of all available ingredients is presented at the website www.concordix.com/customized-formulations#our-ingredients.
The production facilities enable that all supplements are made in an inert atmosphere that minimizes oxidation during the production process, and each raw material is analyzed for oxidation to ensure quality.

4.4 Enhanced Bioavailability

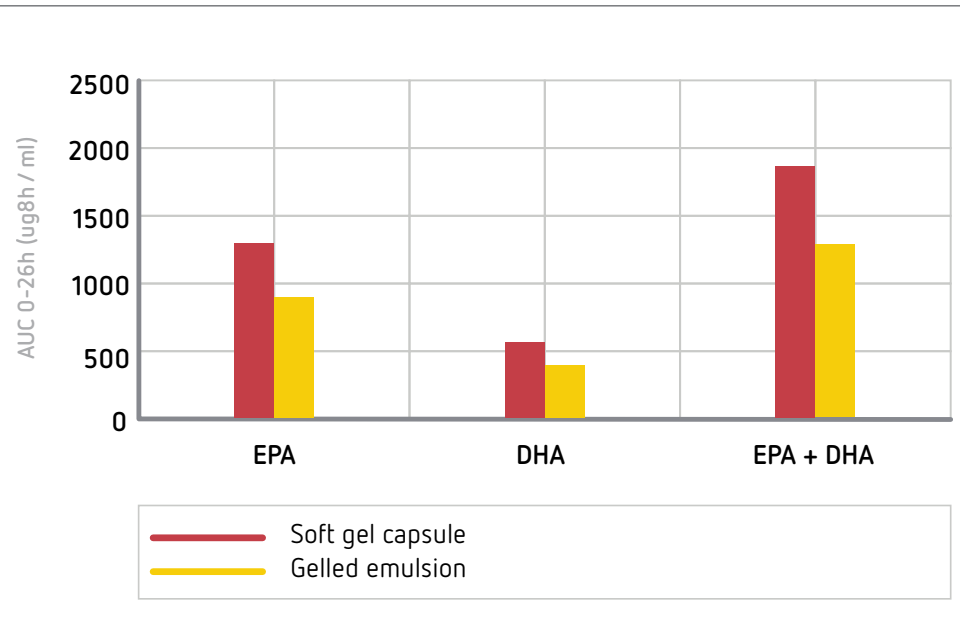
The active ingredients in ConCordix supplements are present as oil droplets (lipid- soluble ingredients) or are dissolved in a lipid carrier further homogenously distributed in the gelatin matrix. This is known as a gelled oil-in-water emulsion. Water-soluble ingredients are easily absorbed in the bloodstream, while this is more challenging for most lipid-soluble ingredients. It is well known that emulsion-based delivery systems, such as ConCordix, can improve the uptake of lipid-soluble ingredients. A study conducted with ConCordix fish oil supplements revealed higher absorption rate (Figure 3) and a 44% increased bioavailability of omega-3 fatty acids compared with a traditional soft-gel capsule (Figure 4). The enhanced bioavailability was attributed to an increased surface area of the dispersed oil droplets, promoting rapid break-down of the omega-3 fatty acids in the fish oil and absorption [11, 15].

Figure 3 Absorption of Omega-3 Fatty Acids Delivered in ConCordix Supplements After 28 Hours



Mean plasma concentrations from time 0-26 h post-administration of omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) delivered by ConCordix or soft gel capsules [11, 15].

Figure 4 Bioavailability of Omega-3 Fatty Acids Using ConCordix Supplements



The incremental area under the curve from time 0 to 26 hours post-administration of omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) delivered by ConCordix or soft gel capsules [11, 15].

Lipid-soluble ingredients may have an improved bioavailability when they are dissolved in a lipid carrier. Typical examples include vitamins such as vitamin E, D and E, but also carotenoids such as lycopene and beta-carotene [16-18]. These ingredients could benefit from being formulated using the ConCordix technology, potentially improving the bioavailability of the active ingredient. Through enhancing bioavailability, the same (health) effects can be achieved with a lower concentration of the ingredient [18]. As a consequence, the size, dosing regime and costs of a dietary supplement can significantly reduce.

4.4.1 Rapid Digestion

The gelatin matrix melts at physiological temperatures and is suitable for releasing active ingredients as soon as it is ingested. The billions of small oily droplets and water-soluble ingredients remain intact in the gelatin matrix during chewing. After ingestion and swallowing, the particles of the supplement containing active ingredients move to the stomach where they are prepared to be further processed by enzymes in the small intestine. The emulsion droplets remain stable when entering the stomach and thereby do not cause gastric reflux of ingredients such as fish oil because they do not create a lipid layer on top of the stomach contents. The brain is triggered to secrete gastric juices and more enzymes that enhance absorption and bioavailability. The unique interface of billions of small oily droplets in the ConCordix emulsion facilitates a large contact surface area between lipid digestive-enzymes. In the small intestine, bile is secreted to act as a surfactant to increase the emulsification of lipids. Because ConCordix supplements contain emulsified oil droplets, the availability for bile salts to create micelles is enhanced. After enzymatic digestion, the nutrients are ready for absorption into the bloodstream. Lipids in the micelles are taken up in the epithelial cells by diffusion across the plasma membrane. Coenzyme Q10 and fat-soluble vitamins A, D, E and K that are encapsulated in the supplements are dissolved in the oil droplets and follow the same digestive path as the lipids in the micelles. A fraction of the fat-soluble vitamins is taken up by simple diffusion and the rest are transported by vitamin-specific transporter proteins. Absorption of water-soluble vitamins is performed by specific mechanisms where selective transporter proteins play a major role. Minerals are taken up by the enterocytes by specific transport mechanisms that are strictly regulated and quite specific for different minerals.

ConCordix formulated supplements are designed to be rapidly digested which results in the complete absorption of ingredients and enhances bioavailability.

5 Customized Formulations

Each supplement can be tailor-made and the list to create a new formulation is endless. A wide range of natural ingredients, including vitamins, essential oils, minerals and antioxidants, as single ingredient or in combination can be provided. In addition, a large variety of flavors, sugar-free sweeteners, colors and shapes are possible.
The size of a ConCordix soft-chew is between 1.2 and 1.7 g and are round or oval shaped.

5.1 Water- and Oil-Soluble Ingredients

The ConCordix technology makes it possible to combine water- and oil-soluble ingredients in one supplement. lipid-soluble ingredients are in general not miscible with water due to the lower density of lipids. The lipid- soluble ingredients are homogenously distributed as billions of droplets in the gelatin matrix which provides a larger contact surface with gastric enzymes making absorption more effective [7].
Some examples of available ConCordix concepts that are produced according to the ConCordix technology:

- VitaCholine contains the water soluble nutrient choline and is combined with fish oil [19].
- Wellmune supplements contain a large concentration of the water-soluble beta-glucan combined with fish oil [20].

A range of available ConCordix concepts is presented at the website www.concordix.com/concept-formulations

5.2 Omega-3 from Fish Oil

ConCordix offers a unique approach to deliver omega-3 fatty acids from fish oil. There are no challenges with oxidation, poor stability, high dosing regiments or large capsules. Because the ConCordix technology offers a unique packaging process, there is no oxidation of fish oil and the soft-chew remains fresh up to the end of shelf-life. Like most other supplements the ConCordix soft-chews need to be stored at room temperature (<25°C) to remain a high quality. A specific flavor profile has been developed to mask the distinct taste and that has a well-accepted taste. Lastly, the unique production technology allows a high payload of the omega-3 fatty acids, resulting in a soft-chew with an acceptable dosing regimen that meets the daily recommended dose.

5.3 Vitamins and Minerals

Vitamins are essential organic nutrients of which most are not produced in the body. Some vitamins are synthesized in the body but only in small quantities. Therefore, the main source to obtain sufficient amounts of vitamins is through a healthy diet. Minerals are inorganic nutrients that similarly to vitamins, are key in ensuring our health and well-being.
We offer a large variety of lipid- and water-soluble vitamins and minerals (www.concordix.com/customized-formulations#our-ingredients) which can be used as single ingredient or in combination with other ingredients. This allows to combine active ingredients that have synergistic effects. Importantly, trends have shown that multi-vitamins are in the top 3 of most used supplements and ConCordix offers a unique delivery system for multi-vitamins.

5.4 Herbal and Essential Oils

Essential oils are the pure, highly concentrated natural constituents that are found in plants. They are used for their healing properties. When used correctly, essential oils bring a wide range of health benefits without side-effects. It is known that essential oils have antioxidant properties and have antimicrobial effects but also potentially reduce viruses and

inflammations [21-23]. Some essential oils have been traditionally used to relieve respiratory tract infections and are currently still used to alleviate colds. Most preparations with essential oils are made for topical administration or for direct inhalation. Alternatives for oral administration are scarce because the volatile components comprise a stable formulation in a solid delivery form.

The ConCordix matrix is perfectly suited for administration of volatile, essential oils. The essential oil is carried in the matrix and upon chewing the soft-chew the volatile oil spreads into the nose area targeting the respiratory tract similarly to traditional inhalation products. The ConCordix technology provides that the soft-chew texture properties can be adjusted to finetune the dissolution rate to adjust the strength of the inhalation effect and its duration. Multiple active ingredients, including botanical and animal derived (propolis) extracts can be combined with essential oils in one soft-chew.

As with essential oils, botanical extracts have great health effects and contain anthocyanins and polyphenols. This is because they are easily digested and absorbed which facilitates rapid action of the botanicals. The bring about changes in the body much quicker than other methods of taking botanicals.

A full list of herbal and essential oils we offer is presented at www.concordix.com/customized-formulations#our-ingredients

Pharmaceuticals

The ConCordix technology opens new possibilities for the pharmaceutical industry. In pharmacy, hard tablets are the main delivery system of use. It is known that large groups of patients have difficulties to swallow large sized tablets or capsules [3, 26]. Especially elderly encounter difficulties with swallowing. As medicine intake often increases in this group, it would be an advantage to provide them with a delivery system that eases swallowing. Studies have shown that people tend to modify the delivery system by crushing or dissolving tablets when they are too hard to swallow. However, this may lead to an erroneous dose that hampers its effects [5, 11].

In addition, many pharmaceutical ingredients have a distinct taste when chewed or solubilized. We have tested if ConCordix soft-chews could mask the taste of ibuprofen. The encapsulated ibuprofen was administered to healthy adults who were instructed to chew 3 or 8 times. Subjects reported that the unpalatable taste was sufficiently masked and that the formulation was very easy to ingest [11]. A statistically significant higher preference ($P < 0.05$) was observed for 3 times chewing over 8 times. In addition, the stability of ibuprofen was exceptional, showing that this delivery system could make a difference in the pharmaceutical industry [27]. Not only homogeneity of the active ingredients is warranted, it may also improve patient compliance and acceptance.

Conclusion

In summary, the benefits ConCordix formulated supplements offer are:

- Great taste – natural fruity flavors and sugar free
- Easy to take – no need to swallow with water
- Daily freshness – unique packaging and exceptional stability
- All in one chew – combination of oil-and water-soluble first-class ingredients and high payload of active ingredients

Besides these benefits, ConCordix soft-chews are developed to make health easier. We strive to make administration as easy as possible and try to produce well accepted tasty supplements to improve long-term compliance.

	Liquid forms		Solid forms				
Characteristics oral delivery forms	Suspension (drinkable)	Elixirs (drinkable)	Tablet / hard capsule	Oro-dispersal	Soft capsule	Gummies	CCx Delivery System
Water soluble ingredients –in form of solution	Yes	Yes	No	No	No	Yes	Yes
Lipid soluble ingredients –in form of solution	**Restricted**	**Restricted**	No	No	Yes	Yes	Yes
Particulate materials	Yes	No	Yes	Yes	Yes	Yes	Yes
Pre-emulsified	**Possible**	No	No	No	No	**Possible**	Yes
Protection from oxidation	**Only until opened**	**Only until opened**	**Extra packing step**	**Extra packing step**	**Extra packing step**	No	Yes
Allowed water content	Yes	Yes	No	No	**Max. 10%**	Yes	Yes
Chewable form	-	-	No	Yes	**Possible**	Yes	Yes
Taste masking / flavouring	Yes	Yes	**Restricted**	**Possible**	**Possible**	**Restricted***	Yes
Easy to swallow / no water needed	Yes	Yes	No	Yes	**No / patient dependent**	Yes	Yes
Sugar free	**Possible**	**Possible**	**Possible**	**Possible**	**Possible**	No	Yes

ConCordix formulated supplements provide a tailor-made solution for the manufacturing of pharmaceuticals and / or nutraceuticals. A wide variety of natural ingredients, flavors, shapes and colors make it possible to develop supplements for human and pet use, all produced according EU food and safety regulations. In addition, similar possibilities are provided for the delivery of pharmaceuticals.

The soft-chews are easy to ingest without the necessity of water, have an excellent taste and taste masking properties and are well accepted across all age groups. The compliance and acceptance rates of ConCordix supplements is high.

Moreover, both oil- and water-soluble ingredients can be combined in one supplement offering a variety of unique opportunities. This delivery system offers a high payload for lipophilic ingredients such as fish oil, compared with alternative delivery forms and has an excellent stability.

At Vitux A.S. we aim to make health easier. We try to provide you with a solution that fits your needs. Vitux A.S. uses state-of-the-art BRC certified manufacturing methods. Only natural ingredients with high quality standards are used to produce turn-key products and customized dietary supplements. A team of experts will assist you to produce a tailor-made product based on your needs. Feel free to get more information about our unique ConCordix soft-chews and visit our website www.concordix.com or contact one of our experts.

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